

FINAL REPORT

December 30, 1991

COOPERATIVE AGREEMENT NCC2-229 BETWEEN NASA/AMES
AND WRIGHT STATE UNIVERSITY

"Evaluation of Putative Neurochemical
Intermediaries in Space/Motion Sickness"

January 1, 1983-December 31, 1985

continued as

"Pharmacological and Neurophysiological Aspects
of Space/Motion Sickness"

January 1, 1986-December 31, 1991

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(NASA-CR-189521) PHARMACOLOGICAL AND
NEUROPHYSIOLOGICAL ASPECTS OF SPACE/MOTION
SICKNESS Final Report, 1 Jan. 1986 - 31 Dec.
1991 (Wright State Univ.) 23 p CSCL 06P

92-14586

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I. Emetic Stimuli.

A. Characterization of the motion stimulus.

A motorized motion testing device modelled after a Ferris wheel was constructed. The cats rode alone in two clear plastic boxes suspended from the ends of a 0.89 m beam that rotated about a horizontal axle. The boxes were counterrotated to keep the floor level. A parametric study determined that the most provocative motion was a frequency of 0.28 Hz (17 rpm), a value similar to that of other species. A standard test was then defined as 30 min of motion at 0.28 Hz followed by one min of observation at rest. Susceptibility was determined in female cats by testing them at two week intervals for five tests. Only those responding on at least two tests were considered adequately susceptible for inclusion in motion studies. Roughly half of the population tested responded on none of the screening tests, while roughly 10% responded at each level of susceptibility, i.e. 10% responded on five of five tests, 10% on four of five, etc (1).

A separate study determined that tests performed at two week intervals resulted in no habituation to the motion stimulus. Five weekly tests resulted in significant habituation and five daily tests resulted in even more rapid habituation. In both cases of habituation, the

susceptibility of the group recovered when tested two weeks later. Further analysis revealed that the rate of habituation was not related to the susceptibility of the subjects (15). In all other motion studies, tests were separated by at least two weeks unless otherwise stated.

The latency to the first retch was verified to fit the Weibull distribution, as it does for human subjects. A program was written to analyze the latency data, fitting it to the two parameter Weibull distribution. Of particular importance was that the program was designed to handle right censored data (when at least one subject does not respond), a situation which applies to virtually every test (6).

B. Xylazine-induced emesis.

A dose-response curve was determined for xylazine administered subcutaneously. The results led to the use of the dose of 0.66 mg/kg as a standard emetic drug challenge in subsequent studies. The emetic effect of xylazine was prevented by the alpha-2 noradrenoceptor antagonist, yohimbine, which did not prevent motion sickness. The asymmetry of the drug response of the two stimuli was also observed for scopolamine, which prevented motion sickness but not xylazine-induced emesis. This result verified that provocative motion and xylazine use different predominant pathways to trigger emesis, as had been suggested based on the observation that xylazine but not motion requires an

intact area postrema for the induction of emesis. The study also observed a correlation between the threshold dose for xylazine-induced emesis and the susceptibility to provocative motion, leading to the suggestion that susceptibility to emetic stimuli in general is a fundamental characteristic of the individual that may occur at the level of the emetic pattern generator (2).

II. Analysis of the constituents of the CSF during motion sickness.

Cannulae were implanted in the rostral portion of the fourth ventricle under appropriate anesthesia and sterile conditions. Samples of CSF were collected at twenty min and again just before motion testing. A third sample was collected immediately after vomiting or after 30 min of motion, whichever occurred first. The fourth and fifth samples were collected at twenty min intervals thereafter. On the day after the motion test, control samples of CSF were collected at the same time intervals and the same time of day.

Analysis by HPLC with coulometric detection (conducted by ESA, Inc) identified 37 compounds in an adequate number of samples for statistical analysis. Most compounds were derivatives of tyrosine or tryptophan. None of the compounds varied as a function of motion testing, either with or without vomiting. However, those cats that did

vomit had lower baseline levels of dopamine and its metabolites, DOPAC and HVA, the serotonin metabolite 5-HIAA, the norepinephrine metabolite MHPGSO₄ and uric acid. Thus, these transmitter systems are likely candidates for a role in the motion sickness process (9). In addition, comparison of the levels of the constituents on the test day with those on the control day which followed, when habituation would have been evident had they been tested, revealed an increase in the minor metabolites 3,4 dihydroxybenzoic acid and 3,4 dihydroxymandelic acid (7).

Another set of CSF samples were sent to NASA Ames for analysis of vasopressin levels. Vasopressin in the CSF did not change as a function of provocative motion with or without vomiting. However, those cats that did vomit had lower baseline levels of vasopressin than did nonresponding ones (4).

III. Evaluation of serotonin-1A (5-HT_{1A}) agonists.

A. Agonist effects on motion sickness.

In a logical follow-up experiment to the CSF analysis, the 5-HT_{1A} partial agonist buspirone was found to block motion sickness (3). Subsequently, three additional agonists also were found to be effective (10,11)(Fig 1). The rank order of potency is roughly the same as their order of binding affinity at the 5-HT_{1A} receptor. The prototype

agonist, 8-OH-DPAT has also been reported to be effective in preventing motion sickness in the Japanese house musk shrew (Matsuki, personal communication). Of the agonists, only buspirone produced nonspecific behavioral effects at doses that suppressed motion sickness and it is the least selective for the 5-HT_{1A} receptor. Unfortunately, it is the only one available for use in human subjects in this country. The only attempt to evaluate the efficacy of buspirone against motion sickness in human subjects used only one dose, 5 mg, which is below the anxiolytic dose range of 20-60 mg/day. The data from the cat make it clear that only doses above the anxiolytic range are effective.

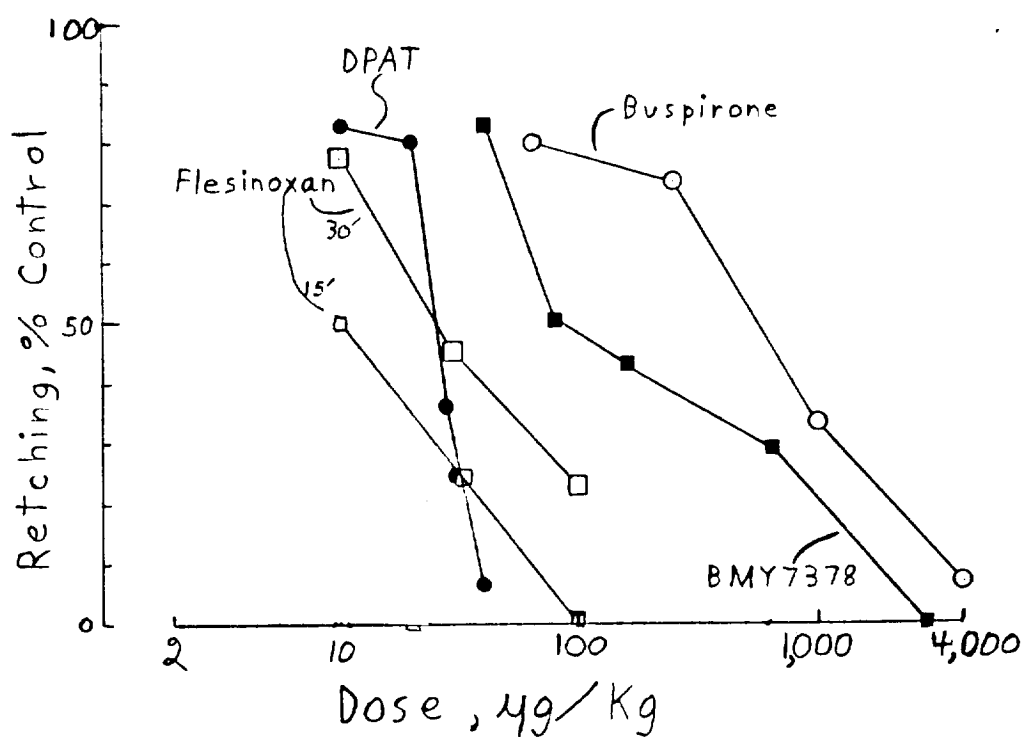


Figure 1. Effects of four 5-HT_{1A} agonists on motion sickness in the cat. Doses are in microgram of drug per kg body weight on a log scale. Flesinoxan dose-response curves were determined twice at different pretreatment times.

The identification of the 5-HT_{1A} site as relevant was verified by reversing the effect of 8-OH-DPAT with the antagonist (-)propranolol (11). Subsequent work demonstrated that the agonists can be differentiated on the basis of the antagonists that are effective in reversing the response. Specifically, the suppression of motion sickness by flesinoxan can not be reversed by (-)propranolol (Table 1). Further, the effect of flesinoxan but not that of 8-OH-DPAT was reduced by the antagonist/partial agonist NAN-190 (Figure 1). This work is providing an important contribution to the understanding of the 5-HT_{1A} receptors and their pharmacology.

Table 1. (-)Propranolol (1.0 mg/kg) did not reverse the effect of flesinoxan. This dose of (-)propranolol previously was determined to shift the DPAT dose-response curve to higher doses (11). All doses in mg/kg.

<u>Treatment</u>	<u>#Retching</u>
Saline	7/10
Sal + prop	9/10
0.10 fles + sal	1/10
0.10 fles + prop	0/10
0.03 fles + sal	2/10
0.03 fles + prop + 30/	1/10
0.03 fles + prop + 45/	2/10
Saline	8/10

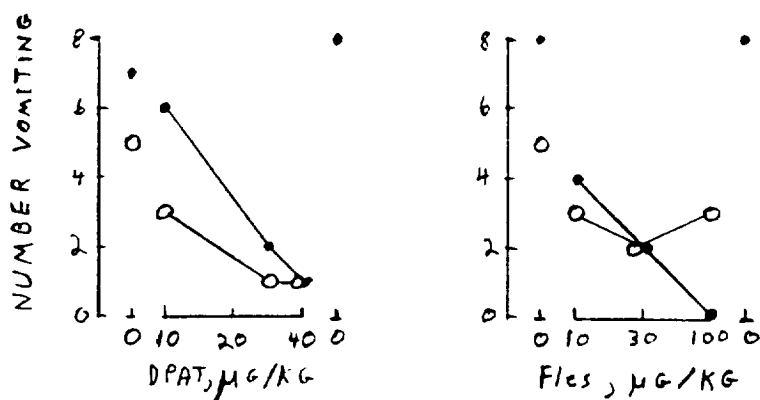


Figure 2. NAN-190 is dose-additive with 8-OH-DPAT but antagonistic to flesinoxan. Solid dots, agonist alone. Open dots, 3 mg/kg of NAN-190 plus treatment on the abscissa. Lower doses of NAN-190 alone and in combination with the agonists had no effect.

B. Relevance of pre- vs postsynaptic sites.

It is of theoretical and practical importance to differentiate between presynaptic and postsynaptic sites of action of the above agonists. Several lines of evidence lead to the conclusion that the relevant sites are located postsynaptically.

Two lines of evidence were obtained by a test of the alternative hypothesis, that 5-HT_{1A} agonists suppressed motion sickness by stimulating presynaptic receptors, leading to a decrease in 5-HT neuronal firing. Attempts were made to mimic the antiemetic effect of the agonists by depleting the 5-HT terminals of 5-HT with the synthesis inhibitor, PCPA, and by blocking the postsynaptic receptors with the nonspecific antagonist, metergoline. With each

drug, there was no antiemetic effect; rather, there was a tendency for increased motion sickness (11).

A third line of evidence was derived from the reversal of the antiemetic effect of 8-OH-DPAT by (-)propranolol. This antagonist has been reported to block postsynaptic receptors but not presynaptic receptors following systemic administration, as was done in the motion sickness experiment (11).

Finally, the results from an experiment with the benzodiazepine, lorazepam are relevant. Doses of lorazepam that decreased motion sickness also produced ataxia. Even higher doses had no effect on xylazine-induced emesis (10). In contrast, 5-HT_{1A} agonists begin to suppress xylazine-induced emesis over the dose range that inhibits motion sickness (3,10). Doses of benzodiazepines that produce ataxia in the cat also completely suppress the firing of 5-HT neurons. Thus, if the 5-HT_{1A} agonists were acting presynaptically to suppress emesis, then lorazepam should also have suppressed xylazine-induced emesis. From the above four lines of reasoning, it is concluded that postsynaptic sites of action are relevant to the antiemetic effect of 5-HT_{1A} agonists.

C. Anatomical location of antiemetic 5-HT_{1A} receptors.

It is also of theoretical and practical importance to determine the anatomical location of the relevant 5-HT_{1A}

receptors. As described below, the most likely site of action is on or near the emetic pattern generator. The broad spectrum of antiemetic effects defies the old conventional wisdom that only those drugs that suppress respiration have a general antiemetic effect. The relevant 5-HT_{1A} sites are currently being further characterized so that they may be used as one marker for the mapping of neurons in the diffusely organized emetic pattern generator.

As described above, motion sickness and xylazine rely on different predominant pathways to trigger the emetic reflex. Both 8-OH-DPAT and buspirone inhibit not only motion sickness but also xylazine-induced emesis (3,10). These agonists suppress cisplatin-induced emesis (5,10), which relies on the area postrema and vagal afferents. 8-OH-DPAT also suppresses emesis elicited by the 5-HT_{1D} agonist, RU 24969 (12) and by orally administered copper sulfate, which relies on vagal afferents. In the latter experiment, the uniformly emetic dose of 10 mg of copper sulfate in 20 ml was administered via a nasogastric tube. The dose of 0.64 mg/kg of 8-OH-DPAT abolished the emetic response. Thus, these agonists exhibit a very wide spectrum of antiemetic effects. The most parsimonious explanation is that the receptors are located on or near the emetic pattern generator.

While unlikely, it is possible that each predominant pathway possesses inhibitory 5-HT_{1A} receptors. If this is the case, then they would act to suppress the vestibular

signal and/or the formation of the mismatch signal. This leads to the prediction that the agonists would interfere with the development of habituation to motion sickness. In a direct test of this interpretation, cats were exposed to three daily tests with provocative motion both with and without suppression of motion sickness by 8-OH-DPAT, and then tested on the fourth day with only administration of saline. The suppression of motion sickness by the agonist did not result in a different incidence of motion sickness than was observed following daily motion without drug. This experiment demonstrated that the inhibitory 5-HT_{1A} sites were located somewhere past the central comparator (e.g. on the emetic pattern generator) and that the emetic response need not be expressed for habituation to provocative motion to occur. These results also demonstrate that suppression of motion sickness by this mechanism during exposure to a provocative environment, such as microgravity, will not interfere with the development of habituation to the emetic stimulus (16).

To summarize, several 5-HT_{1A} agonists suppress motion sickness as well as emesis elicited by a wide range of stimuli. The antiemetic effect may be reversed by 5-HT_{1A} antagonists in a complex manner that may lead to new insights in 5-HT receptor pharmacology. The relevant 5-HT_{1A} receptors are located postsynaptically and are probably to be found on neurons in the emetic pattern generator.

IV. Other 5-HT receptors.

The 5-HT₃ antagonists have been reported to be highly effective in preventing emesis elicited by radiation and by cancer chemotherapeutic drugs. Representatives of this drug class from different chemical families were tested in the cat and found to not prevent either motion sickness or xylazine-induced emesis, even at doses that completely abolished cisplatin-induced emesis (8). This work is consistent with a report that 5-HT₃ antagonists are ineffective in preventing motion sickness in human subjects.

The 5-HT agonist, RU 24969, was found to be an emetic agent in the cat. This action was not mediated through catecholaminergic, 5-HT₂, 5-HT₃, 5-HT_{1A} or 5-HT_{1C} receptors. Because the cat does not have the 5-HT_{1B} receptor, only the 5-HT_{1D} site could have mediated this effect (12). This anatomical location remains unidentified. However, other work in this laboratory has determined that the 5-HT_{1D} agonist, sumatriptan, which does not cross the blood brain barrier, is a powerful emetic in the cat in the dose range of 0.03 to 0.1 mg/kg. Thus, RU 24969 also may exert its emetic action by acting at some site outside of the blood brain barrier. In the course of these investigations, it was observed that the putative nonspecific 5-HT antagonist, methysergide also elicited emesis (11). This drug has been reported to act as an agonist on some 5-HT receptor subtypes in some paradigms. While the relevant site for the emetic

effect of methysergide had not been determined, it is clear that this drug is not suitable for use as an antagonist in the cat.

The 5-HT_{1c} and 5-HT₂ receptor antagonist, mesulergine, did not alter motion sickness in the cat (11), making a role for these receptors unlikely. It has been reported that much higher doses of a 5-HT₂ and alpha adrenoceptor antagonist prevented motion sickness in the Japanese house musk shrew. It is not clear if this discrepancy results from the dose ranges tested, species differences or the presence of an alpha adrenoceptor blockade component. However, 3 mg/kg of the alpha adrenoceptor antagonist, phentolamine, does not alter motion sickness in the cat despite a prominent nictitating membrane response to the drug (unpub. obs.).

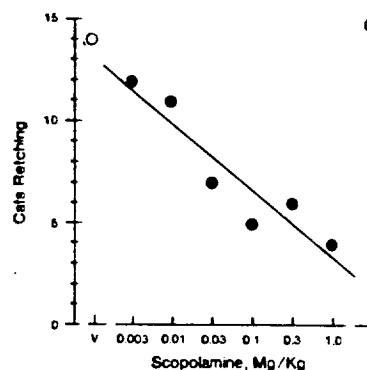
V. Additional studies and activities.

A. Antimuscarinic mechanisms.

The standard motion sickness preventative, scopolamine, was found to inhibit motion sickness (18;Fig 3). In an effort to identify which of the three muscarinic receptor subtypes were involved, the M₁ and M₂ selective antagonist idaverine was tested. Idaverine completely failed to prevent motion sickness over a dose range that had an upper limit due to the appearance of emetic effects. Comparison

of the affinities of scopolamine and idaverine for muscarinic receptor subtypes and the molar doses of each drug used led to the suggestion that blockade of the M₃ subtype is the critical component of the action of scopolamine (17). If subsequent testing confirms this hypothesis, then it will become possible to prevent motion sickness with an M₃ subtype selective antagonist, a drug which will clearly have far fewer side effects than does scopolamine.

Figure 3. Dose-response curve for the suppression of motion sickness by scopolamine.



In addition, a test with the peripherally acting nonspecific muscarinic antagonist, methscopolamine, was performed. While the drug had no effect on the incidence of emesis, it did alter the symptom rating scale. This demonstrates that rating scales use measures that can be blocked by a drug which has no effect on motion-induced vomiting. Thus, the use of rating scales in lieu of an emetic response is highly questionable (18).

B. Antihistaminergic mechanisms.

The common antihistamine, diphenhydramine, did not prevent motion sickness over the dose range tested, despite

the administration of the drug 12 and then again 1 hour before motion testing. However, the histamine synthesis inhibitor, alpha-fluoromethylhistidine, did significantly decrease motion sickness (19). Thus, the histamine transmitter system is involved in feline motion sickness as it is in other species. Further, these results suggest that this synthesis inhibitor may provide greater suppression of motion sickness than standard antihistamines.

C. Amphetamine

Twenty cats received the doses of 0.008, 0.031, 0.125 and 0.5 mg/kg, ten of which received the additional doses of 0.0625, 0.25 and 1.0 mg/kg. None of the doses tested significantly decreased the incidence of motion sickness or significantly increased the latency to the first retch. This is in contrast to recent reports of the effectiveness of sympathomimetics in the alleviation of motion-induced nausea. One possible explanation is that there are species differences. Another possibility is a difference in the measure used. The data from the cat used emetic events as the measure, while recent work with human subjects uses nausea as an end point. The possible confounding by motivational variables in studies with sympathomimetics was suggested in the literature over two decades ago. Early work with sympathomimetic drugs in human subjects which used vomiting as the measure obtained negative results. The reduction of nausea measured by more recent tests would be a

valuable clinical response. However, it is of importance to the NASA mission to determine if sympathomimetics suppress vomiting as well as nausea in human subjects (18).

D. Adenosinergic drugs.

The analysis of the constituents of CSF revealed that levels of uric acid differed in susceptible and nonsusceptible cats. The role and origin of uric acid in the CNS are unknown, but it may be an inactive metabolite of adenosinergic transmission. Accordingly, the role of adenosine receptor subtypes in emetic mechanisms was investigated. The A₁ agonist CHA was found to elicit emesis with a steep dose-response curve, i.e. only one of ten cats vomited at the dose of 0.006 mg/kg, while nine of ten vomited at the dose of 0.01 mg/kg. All ten vomited at the dose of 0.03 mg/kg, with an average of 6 emetic events. The A₁ antagonist CPT abolished the emetic response to 0.01 mg/kg. Emesis elicited by 0.01 mg/kg of CHA was not appreciably reduced by 0.1 or 0.3 mg/kg of the nonspecific adenosine antagonist CGS 15943 and was only marginally reduced by 0.1 mg/kg of the nonspecific antagonist PD 115199.

The somewhat A₂ selective agonist CV 1808 began to elicit emesis at the dose of 0.03 mg/kg and elicited vomiting in eight of ten cats by the dose of 0.3 mg/kg. The emesis was not reduced by 0.3 mg/kg of CPT, 0.1 mg/kg and

0.3 mg/kg of CGS 15943 or 0.03 and 0.1 mg/kg of the somewhat A₂ selective antagonist DPMX. Thus, it is not clear that CV 1808 elicited emesis via adenosinergic mechanisms.

The doses of 0.1 mg/kg of CGS 15943, 0.1 mg/kg of CPT and 0.1 mg/kg of PD 115199 had no effect on motion sickness. There was only a marginal increase in the latency to the first retch following 0.3 mg/kg of CGS 15943 and 0.3 mg/kg of CPT.

In summary, stimulation of A₁ receptors elicits emesis that can be reversed by selective but not by nonselective antagonists. The A₂ agonist tested elicited emesis but the response was not reversed by adenosine antagonists. There was only a marginal reduction in motion sickness following administration of A₁ antagonists, making this mechanism unsuitable for the reduction of motion sickness.

E. Opioid antagonist.

The nonselective opioid antagonist naloxone was tested in ten cats using a 10 min pretreatment time rather than the one hour used in previous tests in the cat. The doses of 0.001 and 0.01 mg/kg had no effect and the dose of 0.1 mg/kg produced a marginal decrease in the latency to the first retch. A previous study by one of the authors (GHC) using different doses and pretreatments obtained larger increases. Thus, nonselective opioid antagonism results in an increase

in motion sickness in cats as it appears to do in human subjects.

F. Peptides.

Continuous infusion of thyroid releasing hormone (TRH) has been reported to enhance the rate of recovery from unilateral labyrinthectomy. To investigate a possible role of TRH in the suppression of motion sickness, stable analogues of TRH must be used because authentic TRH has a half life of only a few minutes following systemic administration. The stable analogue MK 771, in which both end moieties of the tripeptide are substituted, elicited emesis in half the cats at the dose of 0.003 mg/kg and virtually all the cats at 0.01 and 0.1 mg/kg. The monosubstituted stable analogue CG 3703 elicited emesis in three at 0.001 mg/kg, in four at 0.0018 mg/kg and in seven at 0.003 mg/kg. The monosubstituted analogue at the other end moiety was not available for testing to evaluate the role of the end moieties in the emetic response. It is concluded that the stable analogues tested are extremely powerful emetic agents, as TRH itself was subsequently found to be in dogs.

The role of cholecystokinin (CCK) was also investigated using the CCK_A antagonist L 364,718 and the CCK_B antagonist L 364-260. Each compound was tested at the doses of 0.03, 0.1 and 0.3 mg/kg. Neither drug altered either the

incidence or the latency to motion sickness. Both subtypes of CCK receptor were blocked by combining the dose of 0.1 mg/kg of each agent before motion testing. Again, there was no significant effect on motion sickness. This combination was similarly ineffective in preventing xylazine-induced emesis. Thus, CCK does not appear to have a role in motion sickness, though other researchers have clearly implicated it in the suppression of feeding.

G. Cannabinoid

The cannabinoid derivative, N-methyllevantradol, was evaluated for a possible general antiemetic effects, as it has been reported to suppress emesis elicited by cancer chemotherapy in human subjects and in cats. The doses of 0.001, 0.003 and 0.01 mg/kg produced no effect on xylazine-induced emesis, despite the testing of doses that produce measurable inhibition of cisplatin-induced emesis in the cat. The negative results led to the decision to not attempt to prevent motion sickness with the cannabinoid.

H. Cognitive enhancers (nootropics).

Cognitive enhancers (nootropics) improve learning rate, decrease learning deficits elicited by scopolamine or cerebral hypoxia, exert a neuroprotective effect under conditions of metal application or severe hypoxia and exert

anticonvulsant effects. Researchers from the Soviet Union and Eastern block nations report that these drugs reduce motion sickness in human subjects, as do anticonvulsant drugs.

Accordingly, preliminary test were conducted in cats. The doses of 100 and 300 mg/kg of piracetam and 3 and 10 mg/kg of aniracetam had no significant effect on emesis elicited by 0.66 mg/kg of xylazine in cats. In two highly susceptible cats, the dose of 100 mg/kg of piracetam abolished motion sickness. This drug class warrants further investigation as a therapeutic strategy for motion sickness, despite its absence of general antiemetic effects.

I. Dextromethorphan/sigma ligands.

Recently, the dextromethorphan binding site has been characterized as synonymous with the nonpsychotomimetic sigma site. The issue is currently controversial, with possible modulatory roles on glutaminergic transmission described. The antitussives that bind to the dextromethorphan/sigma site also have anticonvulsant effects.

The safe, over-the-counter drugs dextromethorphan and caramiphan, at the doses of 1 and 10 mg/kg, had no effect on xylazine-induced emesis. The doses of 0.3, 1 and 3 mg/kg of dextromethorphan were further tested in the motion sickness paradigm. The doses of 1 and 3 mg/kg marginally reduced the

incidence of emesis and significantly increased the latency to the first emetic event. The dose of 3 mg/kg also produced mild ataxia in the cats. However, the more potent ligand, DTG, had no effect on motion sickness over the dose range of 0.03 to 3.0 mg/kg. On interpretation of this discrepancy arises from a model in which there are four subtypes of sigma receptor. While both dextromethorphan and DTG bind to the sigma-1 receptor, only dextromethorphan bound to the sigma-2 subtype. Thus it is possible ataxia-inducing doses of sigma-2 ligands may moderately suppress motion sickness.

I. Review articles.

Dr. Crampton initiated and edited the book, Motion and Space Sickness, CRC Press, 1990. Both GHC and JBL contributed chapters (13,14). A preliminary review of the 5-HT_{1A} agonist work also appeared in the proceedings of a symposium (20).

K. Role of the cerebellum in motion sickness

Nine motion susceptible cats received lesions of the nodulus and uvula and were tested on the Ferris wheel apparatus for up to nine post operative tests spaced at least two weeks apart. Two of the cats became refractory to motion sickness, and two others displayed a reduced

susceptibility. Preliminary examination of the sectioned and stained brains indicates that only the largest lesions were effective. Further study of the brains is required before a manuscript is prepared.

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